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10/615,560	07/08/2003	Paul C. Ciccolella	3429.1	9011

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EXAMINER	
SALMON, KATHERINE D	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 11/03/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

PTO-90C (Rev. 10/03)

Office Action Summary	Application No. 10/615,560	Applicant(s) CICCOLELLA ET AL.	
	Examiner Katherine Salmon	Art Unit 1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 July 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *08 July 2003* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *03/22/2004*.

4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

5) ☐ Notice of Informal Patent Application (PTO-152)

6) ☐ Other: _____.

DETAILED ACTION

Drawings

1. New corrected drawings in compliance with 37 CFR 1.121(d) are required in this application. The "Description of Drawings" section teaches Figure 2 drawn to a scanning electron microscope image showing different synthesis events, such as no explosure and no biomolecules being synthesized. Figure 2 distinguishes the 2 synthesis events on the SEM image of the array with arrows. The arrow is labeled "no photo-lithography" but fails to distinguish the location on the array where biomolecules are not synthesized.

The "Description of Drawings" section teaches Figure 3 drawn to an example of a misalignment. The specification teaches that the square associated with step 30 is shifted in the x and y directions. The shift is about 3 microns in each direction (p 19 Example 2). The figure is difficult to interpret because there are no labels which with to determine which section has the misalignment. It is unclear where the misalignment has occurred in the figure presented.

The "Description of Drawings" teaches Figure 4 is a scanning electron microscopy image showing a set of Vernier scales designed to detect misalignment (p 3). The scale is unreadable in Figure 4.

Applicant is advised to employ the services of a competent patent draftsperson outside the Office, as the U.S. Patent and Trademark Office no longer prepares new drawings. The corrected drawings are required in reply to the Office action to avoid

abandonment of the application. The requirement for corrected drawings will not be held in abeyance.

Specification

2. Claims should be listed in the specification on a separate page. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claim 12 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term “heavy” in claim 12 is a relative term, which renders the claim indefinite. The term “heavy” is not defined by the claim and the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably appraised of the scope of the invention. There is no clear definition of what a heavy atom would constitute.

Claim Rejections - 35 USC § 102

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claims 1, 2, 8-9, and 11-13 are rejected under 35 U.S.C. 102(b) as being anticipated by Takahagi, et al. (Scanning Electron Microscope Observation of Heterogeneous Three-Dimensional Arrays using DNA May 15 2001 Japanese Journal of Applied Physics, Part 2: Letters p. L521-L523)

Takahagi et al. teaches a fabricating method for a heterogeneous three-dimensional nanoparticle array composed of gold nanoparticles lined by thiol-synthesized DNA oligonucleotide.

With regard to Claims 1 and 2, Takahagi et al. teaches a hybridized solution of DNA (oligonucleotides) and gold (p. L521 2nd column 1st paragraph). Takahagi et al teaches placing a droplet of the hybridized solution onto a silicon substrate (array) (p. L521 last paragraph). Takahagi et al. teaches using a SEM to provide visual evidence of the construction of a nanostructure (p. L521 last paragraph). With regard to Claim 8, the droplet of hybridized solution spread onto the substrate contains gold particles; therefore, it is inherent in the teachings of Takahagi et al. that the slide is covered with a layer of metal.

Claim 9 of the instant application is drawn to a method of exposing a probe on an array with a plurality of targets, scanning the array with a SEM, and detecting the

targets binding to the array. Takayuki et al. teaches that 2 sizes of gold particles (20nm and 9nm) each covered with heptanethiol are mixed together (Figure 1 page L522). The two gold particles are mixed in a hybridization condition (P. L521 2nd paragraph 2nd column). Takayuki et al teaches that a droplet of the hybridized solution comprising a biomolecule probe was cast onto a substrate (i.e. a microarray) (p. L521 last paragraph). Takayuki teaches the two gold particles are attached to the substrate are still in a hybridize solution (p. L521 last paragraph). The molecules are then scanned using SEM to detect binding (p. L521 last paragraph). With regard to Claim 11, the gold particle is hybridized to an oligonucleotide (Figure 1 p. L522). With regard to Claims 12-13, Takahagi teaches an aqueous colloidal gold (Ag) solution containing nanoparticles of 9 nm and 20 nm (P. L521 1st paragraph 2nd column). The claims and the specification fail to define the phrase “heavy atom”. In the instant case, a heavy atom will be defined as gold.

5. Claims 1, 8-9, and 12-14 are rejected under 35 U.S.C. 102(b) as being anticipated by Hermann, et al. (Immunogold labeling in Scanning Electron Microscopy. 1996. Histochem Cell Biol. Vol 106 p. 31).

Hermann et al. teaches a method of using a SEM for 3-dimensional analysis of cell surface events.

Claim 1 of the instant application is drawn to synthesizing biomolecules on a microarray, scanning with a scanning electron microscope, and detecting biomolecules on the microarray. Claim 9 of the instant application is drawn to exposing a biomolecule

probe to a plurality of biomolecule targets under a hybridization condition, scanning the array with a SEM, and detecting targets binding to the probe. Hermann et al. teaches a red blood cell labeled with an antibody coupled to a protein A colloidal gold and scanned by a SEM (Figure 2A). It is inherent in the teachings that the red blood cells would have to be placed on a support in order to be scanned with the SEM. The support with a multitude of cells is considered an array. Hermann et al. teaches antigens (targets) are hybridized to the red blood cell surface (a biomolecule) (Figure 6, p. 35). Hermann et al. teaches scanning the support (i.e. array) with SEM to detect the red blood cells (Figure 2A), thus the red blood cell biomolecule (probes) and the antigen (target) on the microarray are scanned with the SEM.

Hermann et al. teaches a protein A colloidal gold is attached to the antigen (Figure 6 p. 35). In regard to claim 8 is drawn to a microarray coated with a layer of metals, Hermann et al. teaches that the colloidal gold is attached to the antigen which is coupled to the red blood cell on the support (Figure 6 p.35 and Figure 2A). The support (array) would have a layer of gold (metal) coating its surface.

Claims 12-13 are drawn to the labeling of the target with colloidal gold. The claims and the specification fail to define the phrase "heavy atom". In the instant case, a heavy atom will be defined as gold. Hermann et al. teaches colloidal gold can be attached to the antigen (Figure 6 p. 35). Claim 14 is drawn to using a backscattered electron detector (BSE) to detect the heavy atom. Hermann et al. teaches using BSE to detect heavy metal on a biological surface (1st full paragraph p. 34).

6. Claims 1, 8, and 4-6 are rejected under 35 U.S.C. 102(b) as being anticipated by Walt et al. (US Patent 6,210,910, April 3, 2001).

Walt et al teaches a biosensor array in which cells are deployed in a plurality of microwells.

In regard to claim 1, Walt et al. teaches an array of wells in which each well holds a single cell (see Column 11, lines 34 and 42-43). Walt et al. teaches the scanning of the array by SEM (see Figure 4 and Column 10, lines 33-35). Walt et al. teaches that the well size was 7 microns in diameter and 3 microns in depth (see Column 12, lines 18-20). Walt et al. teaches a SEM may be used to characterize the well (see Column 12, lines 21-25). Walt et al. teaches the microwells formed are uniform due to the uniform characteristic structure of the fiber optic array (see Column 12, lines 28-30). It is inherent in the teaching if uniformity of wells can be observed then nonuniformity of wells (errors or misalignments) would be observed and the resolution would be detected would be at least 3 microns. Walt et al. teaches that the surface of the microwell may be coated with a thin film of a metal (Claim 8) (See Column 11, lines 51-54).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the

> subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 1-8 and 9-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over McGall et al. (US Patent 5,843,655 December 1, 1998) in view of Takahagi, et al. (Scanning Electron Microscope Observation of Heterogeneous Three-Dimensional Arrays using DNA May 15 2001 Japanese Journal of Applied Physics, Part 2: Letters p. L521-L523) and McMullan (Scanning Electron Microscopy. 51st Annual Meeting of the Microscopy Society of America, Cincinnati, August 1993. www-g.eng.cam.ac.uk/125/achievements/semhist-intro.com)

McGall et al. teaches an oligonucleotide array which is synthesized by light directed oligonucleotide synthesis (Claims 1-3 of the instant application) (see column 3, lines 37-38 and Figure 2). Claim 4 is drawn to scanning a microarray to detect errors in synthesizing. McGall et al. teaches providing a substrate with two ensembles of

different sequence specific oligonucleotides synthesized by spatially directed oligonucleotide synthesis (see Column 9, lines 15-20). McGall et al. teaches that these two ensembles are exposed to the same test conditions (see Column 9, line 21). McGall teaches test conditions (for example, chemical reagents, exposure to light, acid agent, reducing agent) can be used to test for deprotection (see Column 9, lines 23-25). Detection of testing conditions having an impact on deprotection of the oligonucleotide would show errors between one set of arrays and another. Claim 5 is drawn to detecting a misalignment of the plurality of biomolecules. McGall et al. teaches that biological chips have been produced in which each location has a scale of 10 microns (see column 1, line 23-25). McGall et al. teaches that under selected test conditions, scanning devices can examine each location in the array and determine whether a target molecule has interacted with the probe at that location (see column 1, lines 26-30). With regard to claim 8 McGall et al. teaches that the surface of the solid substrate may be composed of metals (see column 14, lines 33-38).

McGall et al., however, does not teach using a SEM to detect changes in microarrays nor the resolution size of commercially produced SEMs. However, Takahagi et al. does teach using a SEM to detect the construction of a nanostructure (an array) (see p. L521 last paragraph). Takahagi et al. teaches a fabricating method for a heterogeneous three-dimensional nanoparticle array composed of gold nanoparticles lined by thiol-synthesized DNA oligonucleotide. Takahagi et al. teaches a hybridized solution of DNA (oligonucleotides) and gold (p. L521 2nd column 1st paragraph) (Claims 1 and 2). Takahagi et al teaches placing a droplet of the hybridized

solution onto a silicon substrate (array) (p. L521 last paragraph). Takahagi et al. teaches using a SEM to provide visual evidence of the construction of a nanostructure (p. L521 last paragraph). Takayuki et al. teaches that 2 sizes of gold particles (20nm and 9nm) each covered with heptanethiol are mixed together (Figure 1 page L522). The two gold particles are mixed in a hybridization condition (P. L521 2nd paragraph 2nd column). Takayuki et al teaches that a droplet of the hybridized solution comprising a biomolecule probe was cast onto a substrate (i.e. a microarray) (p. L521 last paragraph). Takayuki teaches the two gold particles are attached to the substrate are still in a hybridize solution (p. L521 last paragraph). The molecules are then scanned using SEM to detect binding (p. L521 last paragraph). Takahagi et al. teaches the gold particle is hybridized to an oligonucleotide (Figure 1 p. L522). Takahagi teaches an aqueous colloidal gold (Ag) solution containing nanoparticles of 9 nm and 20 nm (P. L521 1st paragraph 2nd column). The claims and the specification fail to define the phrase “heavy atom”. In the instant case, a heavy atom will be defined as gold.

Takahagi et al. does not teach the typical resolution of commercially available SEMs. McMullan, however, teaches the history of the SEM and the standard resolutions for the microscopes. McMullan teaches that marketed microanalysers (SEM) by 1965 had the resolution of 1 micron (Claims 6 and 7) (see p. 13 McMullan).

Therefore it would have been prime facie obvious to one of ordinary skill in the art at the time the invention was made to improve the method of McGall et al. by including the use of a SEM as taught by Takahagi et al. The ordinary artisan would be motivated to improve the method of McGall et al., by including the use of a SEM,

because Takahagi et al. teaches that using a SEM provides a visual evidence of the construction of a nanostructure (L521 last paragraph). McGall et al. teaches an array in which each individual location of the array is on a scale of 10 microns. The ordinary artisan would have been motivated to observe the individual components of a specific location on the array, therefore, it would be obvious to use any commercially available SEM microscope because McMullan teaches that SEMs have the capability of observing areas as small as 1 micron.

9. Claims 15-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fodor et al. (US Patent 5,424,186 June 13, 1995) in view of Ling et al. (Progress in DNA Chip Technology. March 2001 Chinese Med. Science Journal Vol16 p. 59) and Seiko Epson Corporation (JP2001-176941 06/29/2001).

Fodor et al. teaches a method for synthesizing oligonucleotides on a solid support (an array). Fodor et al. teaches it is possible to direct light to relatively small and precisely known locations on the substrate (see Column 2, lines 62-63). Fodor et al. teaches a method to synthesize polymers of known chemical sequence to known locations on the substrate (see Column 2, lines 64-65). Fodor et al. teaches that one method of light directed synthesis is preformed using masking technology (see Column 4, lines 6-7). Fodor et al. teaches the method of masking allows a ordered formation of a plurality of polymer sequences by the sequential addition of reagents during a step by step method of protecting and deprotecting portions of the sequences attached to the array (see Column 4, lines 6-15).

Fodor et al. does not teach a method for testing for errors in the light directed synthesis process. However, Seiko Epson teaches recognizing differences by generating 2 wafers and analyzing patterns. Seiko Epson teaches a method of recognizing differences in the alignment coordinates of a wafer by analyzing the wafer with a SEM (see Abstract). Seiko Epson teaches that the difference in the alignment coordinate is corrected by temporarily shifting the image data in the point of origin of the chip to the origin coordinate of the defective chip in reference to the defective coordinate data to be superimpose with each other (see Abstract). Seiko et al. teaches using a SEM for high scale factorization of wafers (see Detailed Descriptions paragraph 2). Seiko et al. teaches that the first wafer is optically scanned (see Detailed Descriptions paragraph 3). Seiko et al. teaches that if abnormalities are found then the alignment coordinate is changed based on the defective coordinate data (see Means for solving the problem, Paragraph 10). Seiko Epson teaches using the defective coordinate data to scan for abnormalities in the next chip (see Embodiment of the Invention, Paragraph 12). Seiko Epson does not teach using wafer manufacturing to produce biological arrays. Ling et al., however, teaches that oligonucleotides can be integrated onto the surface of a chip (p. 59 2nd paragraph). Ling et al. teaches one way to fabricate oligonucleotide arrays on a chip is using photolithography (i.e. light directed synthesis) (p. 60 last paragraph, first column). Ling et al. teaches DNA chip technology evolved from computer chip technology in the semiconductor industry (see p. 59 2nd column).

Therefore it would have been prime facie obvious to one of ordinary skill in the art at the time the invention was made to improve the method of Fodor et al. by including the combined teachings of Seiko Epson and Ling et al. The ordinary artisan would be motivated to improve the method of Fodor et al. to include detection of difference in wagers as taught by Seiko Epson because Seiko recognizes defects, such as, difference in alignment coordinates by using a SEM. The ordinary artisan would be motivated to recognize differences in nucleic acid chips using the method of Seiko Epson because Ling et al. teaches that the DNA chip technology industry uses the fabrication techniques of the computer chip in the semiconductor industry (see Ling et al. p. 59).

Double Patenting

10. A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

11. Claims 1-13 and 15-17 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1-12, 16, and 18-20 of copending Application No. 10/835434. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

12.The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

13. Claim 14 is provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 17 of copending Application No. 10/835434. Although the conflicting claims are not identical, they are not patentably distinct from each other because Claim 14 of the instant application is generic to all that is recited in Claim 17 of U.S. Application No. 10/835,434. That is, Claim 17 of '434 falls entirely within the scope of Claim 14, or in other words, Claim 14 is anticipated by Claim 17 of '434. Claim 17 of U.S. Application No. 10/835,434 recites a method where a heavy atom which was enhanced was detected by backscattered electron detector. The instant application's Claim 14 is drawn more broadly to detecting any atom using backscattered electron detector. Thus, Claim 17 of '434 is encompassed by the instant claims.

This is a <u>provisional</u> obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

14. No claims are allowed.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Katherine Salmon whose telephone number is (571) 272-3316. The examiner can normally be reached on Monday -Friday 8AM-430PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones can be reached on (571) 272-0745. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Katherine Salmon 10/31/2005
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Examiner
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